<u>What is Claimed</u>:

1. An aldehyde having the formula:

$$\mathbf{RO\text{-}PAG\text{-}O(CH_2)_z(Y)_m\text{-}\underset{\substack{\|\\ O}}{C}\text{-}X(CH_2)_wCHO} \qquad \textbf{IA}$$

wherein R is hydrogen or lower alkyl, X and Y are individually selected from –O - or - NH- with the proviso that X is NH when m is 1 and Y is –O-, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from about 1,000 to about 100,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, and w is an integer of from 2 to 8, wherein the aldehyde group is free or protected with a hydrolyzable aldehyde protecting group, or a hydrate thereof.

2. The aldehyde of claim 1 wherein said residue is formed from polyethylene glycol.

3. The aldehyde of claim 2 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.

4. The aldehyde of claim 1 wherein said aldehyde has a formula:

$$\mathbf{RO\text{-}PAG\text{-}O(CH_2)_z\text{-}\underset{\substack{\|\\ O}}{C}\text{-}NH\text{-}(CH_2)_wCHO} \qquad \textbf{I-Ai}$$

wherein R, PAG, and w are as above, and z is an integer of from 1 to 4

5. The aldehyde of claim 4 wherein said divalent residue is polyethylene glycol.

6. The aldehyde of claim 5 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.

7. The aldehyde of claim 6 wherein R is methyl and the molecular weight of the residue is about 10,000 Daltons.

8. The aldehyde of claim 6 wherein R is methyl, and the molecular weight of the residue is 20,000 Daltons.

9. The aldehyde of claim 1 wherein said aldehyde has the formula:

$$\mathrm{RO\text{-}PAG\text{-}O(CH_2)_zO\underset{\underset{\displaystyle O}{\|}}{C}NH(CH_2)_wCHO}$$

I-Aii.

wherein R, PAG, and w are as above, and z is an integer of from 2 to 4

10. The aldehyde of claim 9 wherein said divalent residue is formed from polyethylene glycol.

11. The aldehyde of claim 10 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.

12. The aldehyde of claim 11 wherein R is methyl and said residue has a molecular weight of 10,000 Daltons.

13. The aldehyde of claim 1 having the formula:

$$\mathrm{RO\text{-}PAG\text{-}O(CH_2)_zNH\text{-}\underset{\underset{\displaystyle O}{\|}}{C}\text{-}NH\text{-}(CH_2)_wCHO}$$

I-Aiii

wherein R, PAG, and w are as above, and z is an integer of from 2 to 4.

14. The aldehyde of claim 13 wherein said divalent residue is polyethylene glycol.

15. The aldehyde of claim 14 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.

16. The aldehyde of claim 15 wherein R is methyl and the molecular weight of the residue is 10,000 Daltons.

17. The aldehyde of claim 1 having the formula:

$$\mathbf{RO\text{-}PAG\text{-}O(CH_2)_zNH\text{-}\underset{\displaystyle \overset{\|}{O}}{C}\text{-}O\text{-}(CH_2)_wCHO}$$

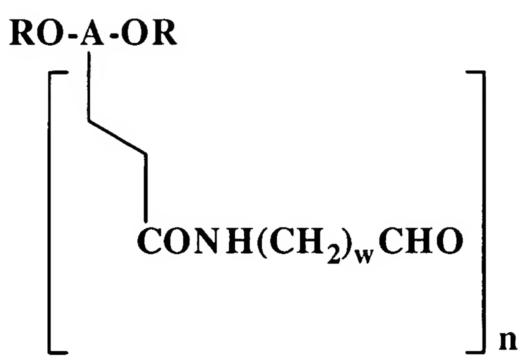
wherein R, PAG, and w are as above, and z is an integer of from 2 to 4. **I-Aiv**

18. The aldehyde of claim 17 wherein said divalent residue is formed from polyethylene glycol.

19. The compound of claim 18 wherein the residue has a molecular weight of 5,000 to 10,000 Daltons.

20. The aldehyde of claim 19 wherein R is methyl and the molecular weight of the residue is 10,000 Daltons.

21. An aldehyde of the formula:



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wherein R is hydroxyl or lower alkyl, A is a polyethylene glycol residue with its two terminal hydroxy groups being removed having a molecular weight of from 1,000 to 100,000 Daltons and having a valence of from 1 to 5, n is an integer of from 1 to 5 which integer is the same as the valence of A, and w is an integer from 2 to 8.

22. The aldehyde of claim 21 wherein A is a residue having a molecular weight of from 5,000 to 50,000 Daltons.

23. The aldehyde of claim 22 where n is 1.

24. The aldehyde of claim 23 where the R is methyl and A has a molecular weight of about 20,000 Daltons.

25. The aldehyde of claim 23 wherein R is methyl and A has a molecular weight of 10,000 Daltons.

26. An aldehyde of the formula:

$$\mathrm{RO\text{-}PAG^{1}\text{-}O(CH_2)_z\text{-}O\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}NH\text{-}\underset{}{\overset{\overset{\displaystyle O\text{-}PAG^{2}\text{-}OR^{1}}{|}}{\overset{(CH_2)_p}{\overset{|}{C}}}}H\text{-}CONH(CH_2)_wCHO} \qquad \mathbf{IC}$$

wherein PAG^1 and PAG^2 are independently divalent residues of poly lower alkylene glycol resulting from removal of the two terminal hydroxy groups with the PAG^1 and PAG^2 residues having a combined molecular weight of from 1,000 to 100,000 Daltons, R and R^1 are individually lower alkyl or hydrogen, z is an integer of from 2 to 4, p is an integer of from 2 to 5, and w is an integer of

from 2 to 8, wherein the aldehyde group is free or protected with a hydrolyzable aldehyde protecting group, or a hydrate thereof.

27. The aldehyde of claim 26 wherein said R is methyl, PAG^1 and PAG^2 are formed from polyethylene glycol residues.

28. The aldehyde of claim 27 wherein R is methyl and PAG^1 and PAG^2 both have a molecular weight of 5,000 to 50,000 Daltons.

29. A compound of the formula:

$$\mathbf{RO\text{-}PAG\text{-}O(CH_2)_z(Y)_m\text{-}\underset{\underset{O}{\|}}{C}\text{-}X(CH_2)_wR^2}$$

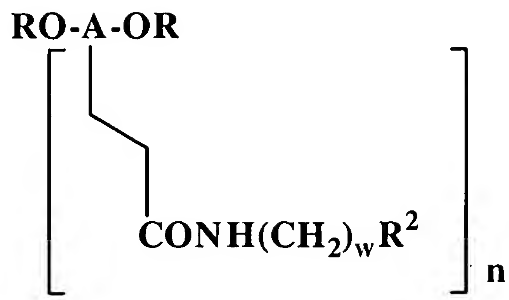
wherein R is hydrogen or lower alkyl, R^2 is $-CH(OH)CH(OH)R_{13}$ wherein R_{13} is hydrogen, alkyl, or phenyl, X and Y are individually selected from -O- or -NH- with the proviso that X is NH when m is 1 and Y is -O-, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from about 1,000 to about 100,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, and w is an integer of from 2 to 8.

30. The conjugate of claim 29 where said conjugate has the formula:

$$\mathbf{RO\text{-}PAG\text{-}O(CH_2)_z\text{-}\underset{\underset{O}{\|}}{C}\text{-}NH\text{-}(CH_2)_wR^2}$$

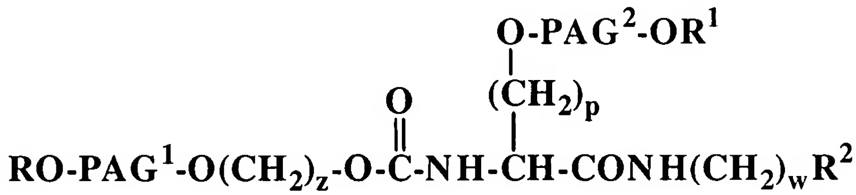
wherein PAG, R, R^2, z and w are as above.

31. A compound of the formula:



wherein R is hydrogen or lower alkyl, R^2 is $-CH(OH)CH(OH)R_{13}$ wherein R_{13} is hydrogen, alkyl, or phenyl, A is a polyethylene glycol residue with its two terminal hydroxy groups being removed having a molecular weight of from 1,000 to 100,000 Daltons and having a valence of from 1 to 5, n is an integer of from 1 to 5 which integer is the same as the valence of A, and w is as integer of from 2 to 8.

32. A compound of the formula:



wherein PAG^1 and PAG^2 are independently divalent residues of poly lower alkylene glycol resulting from removal of the two terminal hydroxy groups with the PAG^1 and PAG^2 residues having a combined molecular weight of from 1,000 to 100,000 Daltons, R and R^1 are individually lower alkyl or hydrogen, R^2 is $CH(OH)CH(OH)R_{13}$ wherein R_{13} is hydrogen, alkyl, or phenyl, w is an integer from 2 to 8, p is an integer of from 2 to 5, and z is an integer of from 2 to 4.

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33. A compound of the formula:

$$\mathbf{RO\text{-}PAG\text{-}O(CH_2)_z\text{-}O\text{-}(CH_2)_w\text{-}R^2}$$

wherein R is lower alkyl or hydrogen, R^2 is $-CH(OH)CH(OH)R_{13}$ wherein R_{13} is hydrogen, alkyl, or phenyl, PAG is the divalent residue of polyethylene glycol resulting from removal of the two terminal hydroxy groups having a molecular weight of from 1,000 to 100,000 Daltons, z is a integer of from 2 to 4 and w is an integer of from 2 to 8.

34. A conjugate of the formula:

$$\mathbf{RO\text{-}PAG\text{-}O(CH_2)_z(Y)_m\text{-}\underset{\underset{\displaystyle O}{\|}}{C}\text{-}X\text{-}(CH_2)_wCH_2NHP} \qquad \textbf{III-A}$$

wherein P is the residue of a protein with its amino group removed, R is hydrogen or lower alkyl, X and Y are individually selected from -O- or -NH with the proviso that X is NH when Y is –O-, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups, having a molecular weight of from 1,000 to 100,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, and w is an integer of from 2 to 8.

35. The conjugate of claim 34 where said conjugate has the formula:

$$\mathrm{RO\text{-}PAG\text{-}O(CH_2)_z\text{-}\underset{\underset{\displaystyle O}{\|}}{C}\text{-}NH\text{-}(CH_2)_wCH_2NHP}$$

III-E

wherein P, R, PAG, z and w are as above.

36. The conjugate of claim 35 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.

37. The conjugate of claim 36 where said P is G-CSF, EPO, IFN-α, IFN-β or Hemoglobin.

38. The conjugate of claim 34 wherein said conjugate has the formula:

$$\mathrm{RO\text{-}PAG\text{-}O(CH_2)_zO\text{-}\underset{\underset{\displaystyle O}{\|}}{C}\text{-}NH\text{-}(CH_2)_wCH_2NHP}$$

III-F

wherein P, R, PAG, and w are as above, and z is an integer of from 2 to 4.

39. The conjugate of claim 38 wherein PAG is polyethylene glycol having a molecular weight of from 5,000 to 50,000.

40. The conjugate of claim 39 where said P is G-CSF, EPO, IFN-α, IFN-β or Hemoglobin.

41. The conjugate of claim 34 wherein said conjugate has the formula:

$$\mathrm{RO\text{-}PAG\text{-}O(CH_2)_zNH\text{-}\underset{\underset{\displaystyle O}{\|}}{C}\text{-}NH\text{-}(CH_2)_wCH_2NHP}$$

III-G

wherein P, R, PAG, and w are as above, and z is an integer of from 2 to 4.

42. The conjugate of claim 41 wherein PAG is polyethylene glycol having a molecular weight of from 5,000 to 50,000.

43. The conjugate of claim 42 where said P is G-CSF, EPO, IFN-α, IFN-β or Hemoglobin.

44. The conjugate of claim 34 wherein said conjugate has the formula:

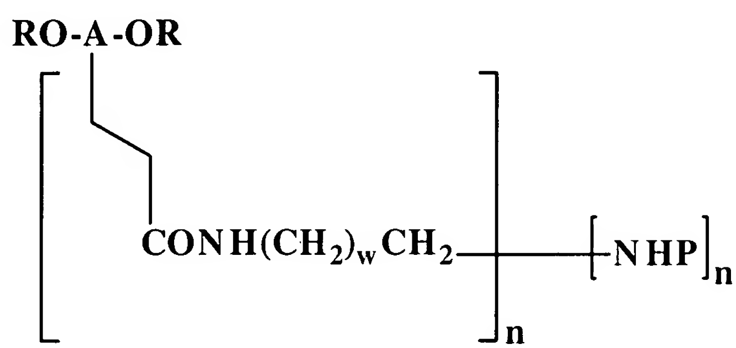
$$\mathbf{RO\text{-}PAG\text{-}O(CH_2)_zNH\text{-}\underset{\underset{O}{\|}}{C}\text{-}O\text{-}(CH_2)_wCH_2NHP} \qquad \textbf{III-H}$$

wherein P, R, PAG, and w are as above, and z is an integer of from 2 to 4.

45. The conjugate of claim 44 wherein PAG is polyethylene glycol having a molecular weight of from 5,000 to 50,000 Daltons.

46. The conjugate of claim 45 where said P is G-CSF, EPO, IFN-α, IFN-β or hemoglobin.

47. A conjugate of the formula:



III-B

wherein P is a residue of a protein with its amino group removed, R is hydrogen or lower alkyl, A is a polyethylene glycol residue with its two terminal hydroxy groups being removed having a molecular weight of from 1,000 to 100,000 Daltons and having a valence of from 1 to 5, n is an integer of from 1 to 5 which integer

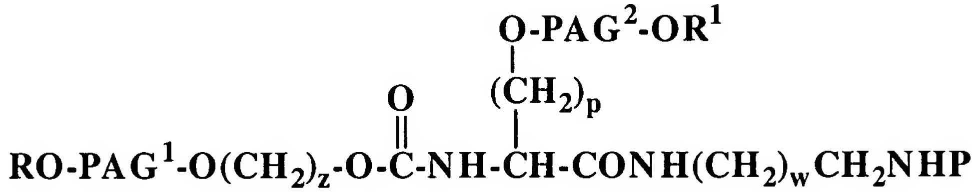
is the same as the valence of A, and which integer is the same as the number of proteins P, w is as above.

48. The conjugate of claim 47 where n is 1.

49. The conjugate of claim 47 where A is polyethylene glycol residue.

50. The conjugate of claim 49 wherein PAG is polyethylene glycol having a molecular weight of from 5 to 50,000 Daltons.

51. A conjugate with the formula:



III-C

wherein P is a residue of a protein with its amino group being removed, PAG^1 and PAG^2 are independently divalent residues of poly lower alkylene glycol resulting from removal of the two terminal hydroxy groups and with the PAG^1 and PAG^2 residues having a combined molecular weight of from 1,000 to 100,000 Daltons, R and R^1 are individually lower alkyl or hydrogen, w is an integer of from 2 to 8, p is an integer of from 2 to 5, and z is an integer of from 2 to 4.

52. The conjugate of claim 51 where PAG^1 and PAG^2 are each polyethylene glycol having a combined molecular weight from 5,000 to 50,000.

53. A conjugate of the formula:

$$RO\text{-}PAG\text{-}O(CH_2)_zO\text{-}(CH_2)_wCH_2NHP$$

III-D

wherein P is a residue of a protein with an amino group being removed, PAG is a divalent residue of a poly lower alkylene glycol resulting from removal of the two terminal hydroxy groups having a molecular weight of from 1,000 to 100,000 Daltons, R is lower alkyl or hydrogen, w is an integer from 2 to 8 and z is an integer from 2 to 4.

54. The conjugate of claim 53 where PAG is a polyethylene glycol residue.

55. The conjugate of claim 54 where PAG has a molecular weight of from 5,000 to 50,000 Daltons.

56. A process for producing an aldehyde of the formula:

$$RO\text{-}PAG\text{-}O\text{-}(CH_2)_z\text{-}O\text{-}(CH_2)_w\text{-}CHO$$

wherein R is lower alkyl, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups, having a molecular weight of from 1,000 to 100,000 Daltons, z is an integer of from 2 to 4, and w is an integer of from 2 to 8;

from a hydroxy compound of the formula

$$RO\text{-}PAG\text{-}O\text{-}(CH_2)_z\text{-}OH$$

wherein R, PAG are as above, and z is an integer of from 2 to 4; comprising esterifying said hydroxy compound to form an ester of the formula;

$$RO\text{-}PAG\text{-}O\text{-}(CH_2)_z\text{-}OL$$

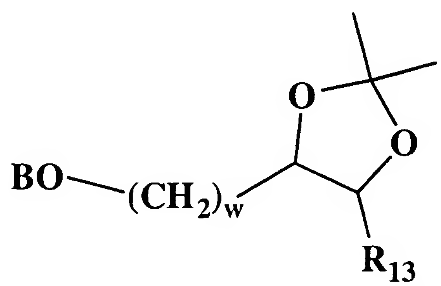
wherein R and PAG are as above and OL is a sulfonic acid ester;

by reacting said hydroxy compound with a sulfonating agent having the formula

$$\mathbf{HaloL}$$

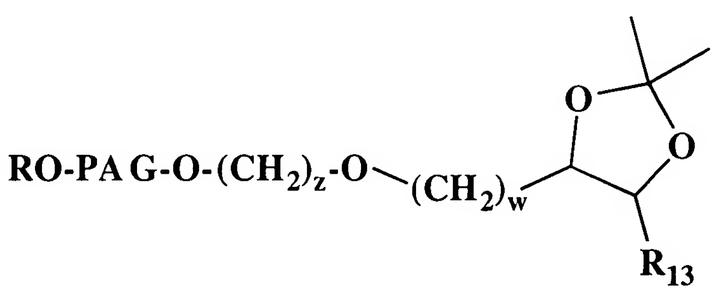
wherein L is a sulfonyl leaving group and Halo is a halogen;

to form said sulfonate ester, and reacting said ester with an acetonide of the formula



wherein R_{13} is hydrogen, alkyl, or phenyl, w is as above and B is an alkali metal;

to form a polymeric acetonide of the formula



wherein R, PAG, R_{13}, z and w are as above;

and thereafter hydrolyzing said polymeric acetonide under acid conditions to remove the acetonide group, and thereafter subjecting said hydrolyzed acetonide to oxidation with a periodate oxidizing agent to form said aldehyde.

57. A process for producing an aldehyde of the formula:

$$RO\text{-}PAG\text{-}O\text{-}(CH_2)_z\text{-}O\text{-}(CH_2)_w\text{-}CHO$$

wherein R is lower alkyl, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups, having a molecular weight of from 1,000 to 100,000 Daltons, z is an integer of from 2 to 4, and w is an integer of from 2 to 8;

from a hydroxy compound of the formula

$$RO\text{-}PAG\text{-}O\text{-}(CH_2)_z\text{-}OH$$

wherein R, PAG and z are as above;

comprising halogenating said hydroxy compound to form a halide of the formula

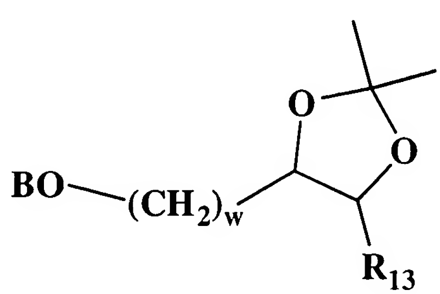
$$RO\text{-}PAG\text{-}O\text{-}(CH_2)_z\text{-}X$$

by reacting said hydroxy compound with a halogenating agent having the formula

$$X_2SO$$

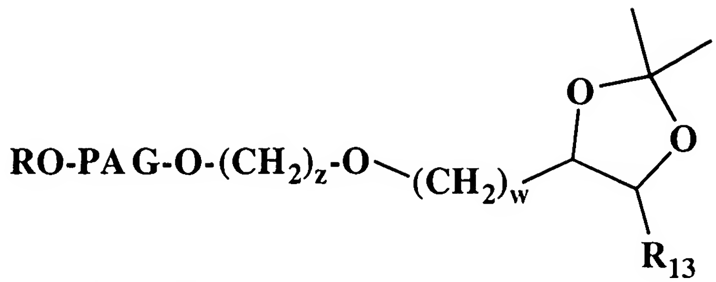
wherein X is a halogen;

to form said halide, and reacting said halide with an acetonide of the formula



wherein R_{13} is hydrogen, alkyl, or phenyl, w is as above and B is an alkali metal;

to form a polymeric acetonide of the formula



wherein R, R_{13}, PAG, z and w are as above;

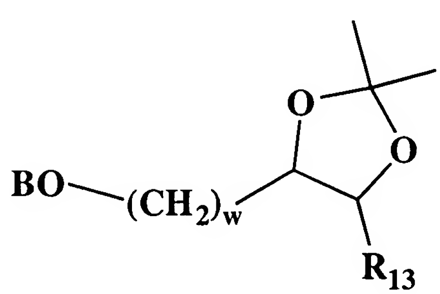
and thereafter hydrolyzing said polymeric acetonide under acid conditions to remove the acetonide group, and thereafter subjecting said hydrolyzed acetonide to oxidation with a periodate oxidizing agent to form said aldehyde.

58. A process for producing an aldehyde of the formula:

$$RO\text{-}PEG\text{-}O\text{-}(CH_2)_z\text{-}O\text{-}(CH_2)_w\text{-}CHO$$

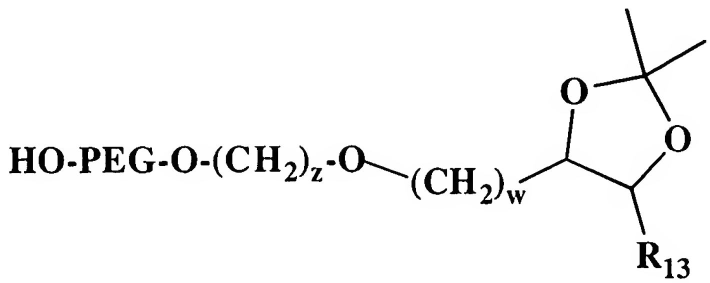
wherein PEG is a divalent residue of polyethylene glycol resulting from removal of the terminal hydroxy groups, having a molecular weight of from 1,000 to 100,000 Daltons, and w is an integer of from 2 to 8, and z is an integer of from 2 to 4.

from an acetonide of the formula



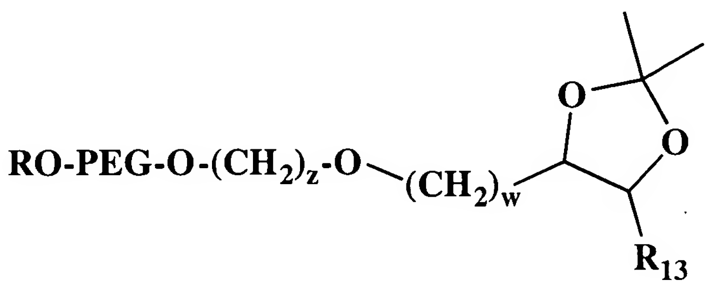
wherein B is an alkali metal, and R_{13} and w are as above;

comprising reacting said acetonide with ethylene oxide by passing liquid ethylene oxide into an organic solution containing the acetonide under polymerization conditions to form the hydroxy acetonide compound of the formula



wherein PEG, R_{13}, z and w are as above;

etherifying said hydroxy acetonide with a lower alkyl halide to form a polymeric acetonide of the formula



wherein R is lower alkyl, and PEG, R_{13}, z and w are as above;

and thereafter hydrolyzing said polymeric acetonide under acid conditions to remove the acetonide group, and thereafter subjecting said hydrolyzed acetonide to oxidation with a periodate oxidizing agent to form said aldehyde.

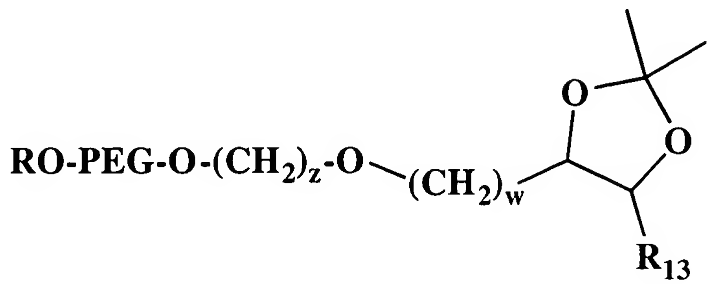
59. A process for producing an aldehyde of the formula:

$$RO\text{-}PEG\text{-}O\text{-}(CH_2)_z\text{-}O\text{-}(CH_2)_w\text{-}CHO$$

wherein PEG is a divalent residue of polyethylene glycol resulting from removal of the terminal hydroxy groups, having a molecular

weight of from 1,000 to 100,000 Daltons, z is an integer of from 2 to 4, and w is an integer of from 2 to 8;

from a polymeric acetonide of the formula



wherein R, PEG, $R_{13,}$ z and w are as above;

and thereafter hydrolyzing said polymeric acetonide under acid conditions to remove the acetonide group, and thereafter subjecting said hydrolyzed acetonide to oxidation with a periodate oxidizing agent to form said aldehyde.

60. An aldehyde of the formula:

$$RO\text{-}PAG\text{-}O\text{-}(CH_2)_z\text{-}O\text{-}(CH_2)_w\text{-}CHO$$

wherein R is lower alkyl, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups, having a molecular weight of from 1,000 to 100,000 Daltons, z is an integer of from 2 to 4, and w is an integer of from 2 to 8.

61. The aldehyde of claim 60 wherein said divalent residue is formed from polyethylene glycol.

62. The aldehyde of claim 61 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.

63. The aldehyde of claim 62 wherein R is methyl and said residue has a molecular weight of 20,000 Daltons.

64. The conjugate of the formula:

$$\mathrm{RO\text{-}PAG\text{-}OCH_2\text{-}\underset{\underset{\displaystyle O}{\|}}{C}\text{-}NH\text{-}(CH_2)_wCH_2NHP} \qquad \textbf{I-Ai}$$

wherein R is hydrogen or lower alkyl, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 1,000 to 100,000 Daltons, and w is an integer of from 2 to 8.

65. The aldehyde of claim 64 wherein said divalent residue is polyethylene glycol.

66. The aldehyde of claim 65 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.

67. The aldehyde of claim 66 wherein R is methyl, and the molecular weight of the residue is about 10,000 Daltons.

68. The aldehyde of claim 67 wherein R is methyl, and the molecular weight of the residue is about 20,000 Daltons.

69. The conjugate of the formula:

$$\mathrm{RO\text{-}PAG\text{-}OCH_2\text{-}\underset{\underset{\displaystyle O}{\|}}{C}\text{-}NH\text{-}(CH_2)_wR_2}$$

wherein PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 1,000 to 100,000 Daltons, R is lower alkyl or hydrogen, R^2 is $CH(OH)CH(OH)R_{13}$ wherein R_{13} is

hydrogen, alkyl, or phenyl, and w is an integer of from 2 to 8 and are as above.

70. The conjugate of the formula:

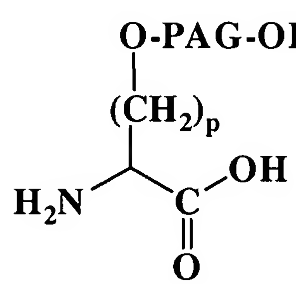
$$\mathrm{RO\text{-}PAG\text{-}OCH_2\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}NH\text{-}(CH_2)_w CH_2NHP} \qquad \text{III-E}$$

wherein P is a residue of a protein with its amino group being removed, R is hydrogen or lower alkyl, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups, having a combined molecular weight of from 1,000 to 100,000 Daltons, w is an integer of from 2 to 8 and are as above.

71. The conjugate of claim 70 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.

72. The conjugate of claim 70 where P is G-CSF, EPO, IFN-α, IFN-β, or Hemoglobin.

73. A compound of the formula:



wherein R^1 is lower alkyl, or hydrogen, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal

hydroxy groups, having a combined molecular weight of from 1,000 to 100,000 Daltons, and p is an integer of from 2 to 5.

74. The conjugate of claim 73 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.